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IMMUNOLOGICAL RESPONSE TO SARS-Cov 2 AND IMMUNOPATHOLOGY OF COVID-19 INFECTION

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Abstract

SARS-CoV-2 is a new beta coronavirus, similar to SARS-CoV-1, that emerged at the end of 2019 in the Hubei province of
China. It is responsible for coronavirus disease 2019 (COVID-19), which was declared a pandemic by the World Health
Organization on March 11, 2020. The ability to gain quick control of the pandemic has been hampered by a lack of detailed knowledge about SARS-CoV-2-host interactions, mainly in relation to viral biology and host immune response. The rapid clinical course seen in COVID-19 indicates that infection control in asymptomatic patients or patients with mild disease is probably due to the innate immune response, as, considering that SARS -CoV-2 is new to humans, an effective adaptive response would not be expected to occur until approximately 2---3 weeks after contact with the virus. Antiviral innate immunity has humoral components (complement and coagulation -fibrinolysis systems, soluble proteins that recognize glycans on cell surface, interferons, chemokines, and naturally occurring antibodies) and cellular components (natural killer cells and other innate lymphocytes). Failure of this system would pave the way for uncontrolled viral replication in the airways and the mounting of an adaptive immune response, potentially amplified by an inflammatory cascade. Severe COVID-19 appears to be due not only to viral infection but also to a dysregulated immune and inflammatory response. In this paper, the authors review the most recent publications on the immunobiology of SARS-CoV-2, virus interactions with target cells, and host immune responses, and highlight possible associations between deficient innate and acquired immune responses and disease progression and mortality. Immunotherapeutic strategies targeting both the virus and dysfunctional immune responses are also addressed.

Key words: ACE-2, ARDS, Acute Respiratory Distress syndrome; C, Complement Factor(e.g., C3a, C3b, C4, C5, C5a); CoV, coronaviruses; COVID-19, DAMPs, Damage-Associated Molecular Patterns; ICs, immune complexes.

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Introduction

SARS - CoV2 Virus

Definition

From the city of Wuhan an outbreak of pneumonia occurred, by the end of 2019. Sequential metagenomic for tested patients' samples showed a genuine Coronavirus with high similarity to SARS genomic sequence [1], the causative agent of minor epidemics in the beginnings & 2000s [2].

This genuine virus was called SARS-CoV-2, because of the similarities in clinical presentation & genomic sequence SAR-CoV-2 induced disease, it was and still commonly called COVID-19. Since the outbreak and till the moment of writing this review, nearly ((474,731,929 million)) COVID -19 cases has seen documented through the world, with nearly ((6,122,496 million)) cases of mortality[3]. These two statistical numbers don`t reflect the true epidemiological extent of the pandemic, it`s estimate that beyond these numbers of deaths may have occurred, especially vaccination is not well established globally and disease is still evolving and higher endemicity levels are becoming established. Even though the mortality rate from SARS COV-2 is way lower than the infected with SARS COV-19 [4].

Pharmaceutical methods and procedures failed to quarantine the disease and control the pandemic. notably prior to onset of symptom the infectivity and viral load usually peaks in the infected people [5], this will render quarantine and other counter measures ineffective at controlling illness in society.

Coronavirus a variable category of RNA viruses' family of single strand genome, infecting diverse types of vertebrates. First, they were isolated in humans around 1960s [6], being the agents of cause of simple upper infections. By the early 21th century, a highly violent strains of beta Coronaviruses responsible for new infections from zoonotic sources started to break through. Let`s highlight the first of those, as severe acute respiratory distress syndrome (SARS-COV-1), in early 2002, then the famous middle respiratory syndrome coronavirus (MERS-COV) in 2012, with an estimated mortality for each of (10%-43% in order) [7].

The genomic content of Coronae, it`s a range of 30kb of length, and is mostly enveloped by an outermost fatty lipid layer, to help protecting the virus and evading the host immunological response, this will aids in host cell invasion [10, 11]. Four genera make up the Coronavirinae Subfamily, as (a-CoV, b-CoV, g-CoV, and d-CoV)., coronaviruses[12], those involved in human infections are placed under the genes alpha & beta (SARS & MERS) , with pigs & avian , are more likely being infected by gamma & delta genera [12]. from phylogenetic studies, SARS COV2 was enlisted under the Beta - coronavirus genera, having 88 % Sequence Similarity to SARS - Cov like Coronaviruses (from bats), with 7.9 % similarity to SARS – Cov1 & 50 % Similarly to MERS – CoV [13]. So, we Come up with conclusion that bats are the immediate host by its genomic similarities, then it was transmitted to an unknown transitional host, acted as a point of spread of this virus to human race.

Pathogenicity

Starting from the nasopharyngeal tract, SARS – COV2 follows a path from this area to reach the lungs. upon inhalation, the virus enters host epithelial cells, then engage with ACE2 receptor of the nasopharyngeal epithelia, via it's Receptor Binding Domain surface elements of the virus and multiply [14, 15, 16]. during this period of 1-2 days the virus multiplies Continually in the nasopharynx, with no apparent resistance by the host innate immunity, reflected by an asymptomatic phase of clinical disease. The next 2-14 days of contact with virus, typical COVID-19 symptoms appear, closely resemble those of MERS and SARS, I.e. tiredness, fever, dry cough, Shortness of breath, pharyngitis, joint pain, during this period the Various community Complication appear, as in hospital and fomite transmission of infection, this would further complicate the spread in

Community [17]. a strong immunity will be initiated following the descendance of virus toward the lower respiratory tract via inhalation. Serious complication Start after this point, Severe pro-inflammatory response occurs complicated by viral sepsis, and intense cytokine storm, all results in Pulmonary effusion and edema, organ failure, terminally death [18]. The infected people might not show significant gastrointestinal symptom like diarrhea, as with previous episodes of COVID infections. The most effective measure to limit community spread of the disease is quarantine till

September 2020[19], beyond this date vaccination have proven efficacious at limiting the extent of COVID-19 in the communities[20]. The most complicated forms of COVID-19 are seen in older population and those with defective immune response, like HIV and Chemotherapy patients to some extent those with hypertension, obesity, heart, kidney, diabetic, asthmatic & hepatic disorders, are less but still at certain risk for acquiring the disease[21].

Prevalence

SARS-CoV-2 spread was dramatic, by March 11/2020 it has reached more the 100,000 people all over 100 Country and the world, With more than 4000 deaths Fatalities. It was the first Corona virus associated illness that was declared global pandemic by WHO[22]. wide global spread of infection cases has emerged exponentially since then, due to increased modernization and ease of international travelling. Global measures to bring the disease spread under control was rendered ineffective and limited, due to lack of Complete knowledge about SARS-CoV-2 biology, host immunological response, non-available rapid diagnostic and case confirmatory test, and no effective treatment was available to quarantine the disease, at that time. At this time, the world was racing time to establish a solid understanding of host-virus interaction, to urgently identify reliable and efficient diagnostic, quarantining and therapeutic regimen to control and prevent spread of infection, back then, the scientific & medical community Kept Generating a bank of knowledge & information in at a rapid rate with cooperative sharing across the most variable Scientific publishing sites**23, 24**.

Epidemiology

A pneumonia like Symptoms was urgently reported by the end of December 2019, by a local health authority in the Wuhan City Specifically originating in a Seafood market, that can't be connected to an etiological cause in

Hubei province, China[25]. WHO named the etiological agent as (2019-nCoV) 2019 Novel coronavirus on January 7 2020 [26].

This virus was then enlisted to a systemic name, SARS cov2 by the (CSG coronavirus study group) that belongs to (ICTV international committee on the taxonomy of viruses) [27], in 1/2/2020 in this same day the disease was officially named

COVID-19 [28]. This infection was already announced as (PHEIC public health emergency of international concern), this put SARS Cov2 as the sixth in chronological orders after 1HINI 2009, 2Polio 2014, 3Eobla West African Ebola, 4Zika 2016, 5Ebola of the democratic republic of Congo 2019, it was eventually declared as global pandemic by WHO in March/11/2020 [29] . since November 13 2020, this seriously infectious illness has spread all over the world Countries and territories over the world, with

(474,659,674 million) infection Cases, and (6,103,355 million) deaths worldwide , causing a mortality rate of 6% [30].

Immune response to SARS-Cov2

Upon virus entry into the host call, these cells start recognizing viral Surface protein epitopes, or the entire virus particle, by the host immune system, to trigger innate and

adaptive immune response. Immune cell surface (PRRs pattern recognition receptors), like TLRs, are first to recognize the virus, subsequently interform production is enhanced. The overall cytokine production is compromised, because SARS and MERS nonstructural proteins would seriously Impairs the host innate immunological response [31].

Similar to previous coronaviruses infections, SARS-Cov 2 was found to illicit the same pattern of humoral response in the infected host characterized by typical IgM and IgG responses. Early post Coronavirus infection, viral N protein trigger host B-cell response followed by antibodies production, especially against S protein, this typically become detectable after 4-8 days from symptoms development[32].

Comparatively N protein is of smaller molecular size than that of S protein, still it's be greater immunogenic potential; highly neutralizing Nspecific antibodies would be produced at early stages 2 of the acute disease[33]. Specific IgM, IgG, and IgA to SARS Cov2 has been found in patients' samples after the symptoms appear, still at a different timeline in those Infected people, Typically IgG levels persist over a relatively long time, compared to IgM which levels appears to drop after almost 3 months[34]. From this point, 16 SARS-CoV-2 patients in an observational study, gave the following data, anti-S RBD IgG, was detectable in all patients, anti-N IgG and anti-S RBD IgG were observed in 15 patients only, whereas anti-N IgM in 14 patients only [35]. Another kinetic study based on ELISA-time frame design, to detect COVID-19 distinct humoral immune response, showed the following, the patients developed specific IgM and IgG antibodies, that would not interact with other coronavirus except for SARS Cov1, then within 5 days IgM antibodies become detectable, followed by IgG after 14 days from symptoms onset[36]. Even another kinetic study, directed to viral Shedding & detection of antibodies, reflected that severely infected SARS-COV2 patients had a higher IgG and IgM antibodies detected, whereas weakly responders for IgG against SARS-Cov2 had a more robust clearance of virus compared to high responders. We can make a conclusion that the stronger antibody response the more Severe form of the disease, as compared to those experience better disease outcome due to strong viral elimination by the comparably feeble antibody response[37]. in pediatric population a case study, concluded that a strong neutralizing antibodies IgG and IgM specific to N and S-RBD protein in 5 out of 6 patients that showed a humoral immunity to SARS Cov2[38].

The above Studies placed IgM ELISA as a reliable technique and can be utilized along with qPCR to improve the sensitivity and Specificity of diagnosis.

Beside the protective neutralizing antibodies, that are useful and have a defensive role, on the other hand, Certain non-neutralizing antibodies, within the immune system, would encourage infection by facilitating the APC (antigen presenting cells) immune Cells infection, especially documented viral infection in FcR associated Immune cells, may become target to SARS Cov-l antibodies, & initiate infection[39]. Such path of cellular spread, nondependent on ACE 2 entry it would not aid Viral propagation & multiplication, its considered specially involved with Shedding of virus, to macrophages that would trigger inflammation and myeloid line stimulation to reflect tissue injury. Such direct Stimulation of immune Cells via non-neutralizing antibodies, is called ADE

(Antibody dependent Enhancement) [40]. ADE is a viral associated phenomenon, was observed with SARS and MERS especially anti-S antibodies, that facilitates entry to FcR immune cells[41]. if we consider MERS; then a Synthetic neutralizing Mab (MERSMAB-1), Targets RBD this will competitively block viral entry to host Cell. On the other hand, SARS-CoV2, investigations are underway to develop such MAB inhibitor against viral fusion with ACE-2, and helps Control of the infection[42].

Viral Entry, Innate Recognition & Immune Evasion

Coronavirus lineages & entry receptors

Four subclasses alpha, beta, gamma, and delta are the well-known linages of the positive sense enveloped RNA virus class, Coronaviruses[43].

Beta-coronaviruses included the early SARSCoV1, and MERS Cov, newly the SARS-Cov2 as in the novel virulent cousin was added to them, as well as considering the less pathogenic strains, DC43 & HKU1 these are implicated in common cold conditions. NL63 and 229E are endemic alpha coronaviruses, responsible for common upper respiratory tract infections of mild severity. The prevalent Serology is secondary to exposure to 90%, for OC43, HKUI, NL63, and 225E [44]. to date these are the main strains at Coronavirus of human disease concern.

Generally speaking, all coronaviruses utilize the envelope associated Spike protein to mediate host cell evasion & entry, yet the host cell receptors vary with the strain. for both SARSCov-1 & SARSCov-2 the entry surface receptors are the Angiotensin Converting enzyme 2 [45], where CD 26 for MERS mostly. such differences can be simplified by a distinct disulfide bond in spike of MERS COV that would significantly pushes the extent outermost surface of the receptor attachment domain, creating such tropism [46]. Coming to the alpha coronaviruses NL63, the entry domain to the host cells is still ACE2, even the few sequence similarities with the spike protein of SARS cov2 [47].

Being able to withstand and adapt the mutational impact, coronavirus spike protein presents a great challenge to the humoral immunity, as it`s difficult to adapt to the viral evolution and immune variance escape.

Considering other RNA viruses, hepatitis C and ZIKA, tropism is not just a function of entry binding receptor only, still other factors need to be considered. Taking ZIKA virus as example, these viruses counteract human STAT2, not the mice STAT2 [48], this would make mice unsusceptible to ZIKA infection.

Now, let`s go back to coronaviruses, in Bats it`s the most critical and actually the only step is the binding to ACE2 receptor, for initiating infectivity and transmissibility [49].

Recently with SARS Cov2, the greatest problem was encountered when we found that SARS COV virus has a binding affinity of greater than

15nm to ACE, 20 time more than that of SARS COV 1, to ACE receptor[50].

In previous studies, it was noted that only binding to entry receptor are the primary and the very most important barrier for initiating infection, and species selective tropism, would specify animal reservoirs like Bats and others, reflects the greatest threat to any community as it presents the threat of pandemic outbreak in the world at any time.

The innate Recognition

Innate immunity has several humoral components, including element of the complement component, fibrinolysis coagulation system, soluble proteins that detects cell surface glycans, (MBL, IFN, chemokine, natural antibodies like IgM, IgA, IgG), with critical cellular elements, such as Natural killer cells, lymphoid cells, alpha gamma cells, that attacks target cells, thereby control the spread of viral infection by direct cell cytotoxic action, as well as triggering an adaptive element of immune response. Various aspects of viral biology can be altered by viral surface glycosylation, such as cellular tropism, recognition by immune processes, surface protein elements stabilization, masking of antigens normally neutralized by circulating antibodies. In a recent study, it was found that mutation in a distant site (10 nm far from receptor binding domain RBD) would affect SARS COV2 ACE2 affinity of binding, such as polybasic site of cleavage is a design target, for possible future neutralizing SARS COV2 binding to its receptor [51].

Neutralizing Antibodies

A class of antiglycan antibodies, like ABO antibodies, they belong to IgM class, naturally detected in serum, presence might shed some light about the past and clinical severity of past coronavirus infections [52]. Normally there is a drop in the circulating levels significantly with >40 years, and physiologically less in blood group A and in men [53]. Levels

of Anti-A circulating antibodies and chance of SARS COV2 infection probability has been previously correlated as protective [54], however in recent meta-analysis it was found to be statistically non-significant, and further studies needed to establish protection [55].

Complement component

A major element of innate immunity is the complement component, and Mannose binding lectin pathway MBL is a natural member of innate complement component, have a crucial role in SARS COV 2 infections, it detects mannose rich surface residues on the surface of a variety of microorganisms, thereby acting as a soluble Pattern recognition receptors PRRs. Eliciting inflammation and triggering phagocytosis, one major action is detection of SARS COV2 via MBL, then deposition of C4 on the virus, decreasing viral infection capacity[56]. Severity of SARS-COV-2 is linked to serum MBL concentration, as certain genetic defects in MBL concentration, as well as physiological decrease in MBL concentration with age, has shown to reflect higher incidence and more severe pattern of SARSCov2 infection[57].

Interferons and Cytokines

Natural innate defenses against viruses are mediated via the expression of interferons and it`s coordinated response. In case of SARS infections, interferons I and III is the major "innate interferons", in limiting the SARS Cov 2 severity[58]. They establish a cellular resistance state, and trigger adaptive immune response[59]. Once microbial element is encountered, cellular

PRR detects it and induce production of Interferons I and III, this in turn triggers activation and transcription of nuclear factor kB (NF-kB) and interferon regulatory factors. This would collectively trigger the synthesis of proinflammatory cytokines and interferons I and III, then via JAK-STAT signaling pathway, the interferon coding genes would be expressed[59]. SARS-Cov-2 have devised a resistance genetic elements and mechanism to counteract this defense [60].

SARS Cov2 Impact on interferon I and III responses

SARS Cov2 is unique among respiratory viruses as Influenza virus and RSV, in it`s strange transcriptional characteristics, it reflects robust proinflammatory and reactive cytokines and chemokines, with depressed Interferons I and III responses[61]. This was established by comparative serum interferons I and III of SARS Cov2 vs Influenza A viral infected individuals, the results showed it severely depressed concentration[62]. Later on, at advanced stages of infection these Interferon responses become evident in fraction of patients with severe disease state[62]. This patient shows typical delayed but extended course of illness and type I and III interferons with triggered type 2 immunity such as Il-5 and Il-1b[63]. SARS-Cov-2

have the characteristics of distributed IFN 1&3 responses and disease outcomes that reflect a dysregulation in immune response hallmark of cytokine disturbance [64]. such distribution is shared feature of SARS-Cov-2 with SARS-Cov-1 and MERS its cousins[65]. Once it infects the lungs Sars cov suppress IFN I and III response promoting monophilic invasion and lung inflammation with leaking vasculature and blunt T Cell response [66]. in a rat model supplying an exogenous IFN 1 would decrease lung pathology significantly[66]. this establishment of delayed IFN response is fixed that reflect a great impact on disease pathology and failure of bringing the viral replication under control in early stages of disease.

This response blunting was found to be induced by virus and the host additional factors, as SARS will encode for antagonists that blocks IFN responses at different stages[67]. Firstly, Virus blocks recognition of Rig-1 and MDA5 of viral RNA, by masking their 50 ends through guanine N7 methyltransferase and 20-Omethyltransferase action[68]. In addition,

excess production of nucleocapsid protein and nsp5 that blocks Rig-1 by blocking the TRIM25 induced ubiquitination [69].

N and M proteins in membrane can block macromolecular aggregates of MAVS, as an essential adaptor of Rig-1 like receptors [70]. Similarly, ORF9b blocks type 1 IFN stimulation, by blocking the ubiquitination of IKK¥, were nsp6 and nsp13 bind to TBK1 to block the phosphorylation of IRF3 [71]

Performance evaluation of Elisa kits for IgG detection of SARS-cov2

In the article chosen, the performance of a marketed Elisa kits was tested comparatively to detect SARS-CoV-2 2 infected patients' samples from 101 patients' samples against 70 control samples form patients as healthy blood donors, this article studied the specificity, sensitivity, positivity, negativity predictive values at variable timelines form the symptom onset (7,8-14 and 14 days) to individual kit.

The results came indicating that all kits gave a remarkable performance during the early first week after onset of symptoms compared to similar studies [72]

As expected, the coincidence between the outcome for each Kit and PCR proportionally increased with symptoms initiation, it was coincident with the lag period from symptoms onset and observation of detectable AB. Higher rate of positivity was reached after the early first week of illness[73]. Regarding the sensitivity breakpoint the lowest values was observed at early stages, but significantly improved at 14 days post onset of symptoms. Anshlabs was the kit of the greatest sensitivity in people tested with the first 20 days from appearance of symptoms.

still, it had the least specificity as compared to other kits. Beyond 14 days sensitivity dropped observably except NovaTec and lionex. notably some patients didn't show any response by all kits, and these people need other highly sensitive procedures to reflect data.

one observation was a healthy control sample was positive for anti MERS AB was positive in these kits, except for Lionex that show 98.6% specificity.

Observation was noted in regards of heterogeneity of IgG assays that targets different areas of virus, the observation showed that (anti-N) AB appeared early compared to (Anti-S) kits, and wane fast comparatively[74].

this was observed in this article too, depending on the type of protein targeted, and it was established that a drop in sensitivity was observed for ELISA Kits that utilize N protein as target, lionex targets S protein that's why the sensitivity increased in this kit remarkably. This reflects the fact that both AB are high early in disease process but drop in Anti N occurs and a weaning response happens [74], this explains Lionex sensitivity compared to others.

Summary, two Kits (Novalisa & Lionex) showed the highest promise as a desirable kit for diagnostic purpose, all kits gave high 85.7 - 98.6% except AnshLabs kit. Even though they would not replace the traditional molecular and PCR method, they are of great importance at establishing the seroprevalence of SARS cov and quantitative determination of extent of herd immunity in population infected [75]

This will bring an easier restriction on humans' mobility and interactions with no eliciting renewal of transmission and mortality. To the moment there is now link between strong immunity detection by ELISA kits and protection against infection in the future[76].

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